Table 4: **Gag**

HXB2 Location	Author Location	Sequence	Immunogen	Species(HLA)	References
Gag( )	p24( )		HIV-1 infection, Vaccine	human( )	[Kelleher1998]

Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17

- Immunization of HIV+ people with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre
- Immunization with p24-VLP showed a modest, short-lived increased proliferative response to p24

Gag( )	p24( )		HIV-1 infection, Vaccine	human( )	[Maino2000]

Vaccine: *Vector/type:* protein, gp120 depleted virus HZ321 (REMUNE^{TM}) *Strain:* Z321 *HIV component:* p24, gp120 depleted virus

- 18 HIV-1-seropositive patients with a low frequency or no detectable CD4+ T-cell response to HIV-1 antigen received an HIV-1 immunogen consisting of 10 units of native p24 and 100 ug of HZ321, a gp120 depleted antigen
- Using flow-cytometric methods, HIV-1 specific CD4+ T-cells were shown to increase in response to immunization – in many patients significant enhancement was observed after a single immunization
- The frequency of CD4+ T-cells expressing cytokines in response to antigen by FACS was correlated with a lymphoproliferation assay

Gag( )	p24( )		HIV-1 infection	human( )	[Ruiz2000]

- Structured treatment interruption in chronically infected patients allowed recovery of p24 Th proliferative responses after HAART therapy discontinuation in 2/12 patients
- The Th response to p24 was identified during peak viremia in one patient, while in the second it was noted when viremia was controlled after restarting antiviral therapy

Gag( )	p24( )		HIV-1 infection	human( )	[Lori1999]

- Ten patients with acute, pre-seroconversion HIV-1 infections were treated with didanosine, indinavir and hydroxyurea – this treatment is associated with normalization of immune parameters
- A vigorous HIV-specific Th response (stimulation index greater than 8) was observed in 7/8 patients treated before complete WB seroconversion, but in only 1/5 controls treated after seroconversion
- Vigorous Th responses were detected as early as 34 days after treatment begin
- Patients treated prior to seroconversion had no loss of naive CD4 T lymphocytes, recovery of up to 35% of the naive CD8 cells in several weeks, and a reduced latent viral reservoir

Gag( )	p24( )		HIV-1 infection	human( )	[Haslett2000]

- 11/22 adult patients on HAART showed strong CD4+ T-cell IFN-γ producing Th1 responses to HIV p24
- The magnitude of the Th1 response correlated with previous interruptions in HAART, suggesting the interruptions primed or boosted the response
- In contrast, the magnitude of the CD8+ CTL response did not correlate with interruptions in therapy, although a greater breadth in response was associated with interruptions in HAART

Gag( )	p24( )	HIV-1 infection, Vaccine	human( )	[Klein1996a]

Vaccine: *Vector/type:* virus-like particle *HIV component:* p24, p17

- Immunization of HIV+ people with a HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load
- Two of four subjects that received 500 or 1000 ug of p24-VLP had an increase in gag-specific CTL

Gag( )	p24( )	Vaccine	human( )	[Moss1998]

Vaccine: *Vector/type:* gp120 depleted virus HZ321 (REMUNE^{TM}) *Strain:* Z321 *HIV component:* gp120 depleted virus

- Immunization with gp120 depleted HZ321 virus (REMUNE^{TM}) triggered an increase in lymphocyte proliferative response to native p24, a clade B virus and clade E viral antigens – Z321 is clade A in env and clade G in gag. [Moss1998]

Gag( )	p24( )	HIV-1 infection	human( )	[Rosenberg1999]

- This paper reviews the role of T-cells in viral control and HIV disease outcome
- Strong anti-p24 lymphoproliferative responses were found in seven persons who were treated with potent anti-viral therapy during acute HIV-1 infection syndrome
- This suggests that Th cells are part of the normal response to HIV-1 infection, but their numbers are rapidly diminished by either being infected during the peak viremia or by activation-induced cell death – if peak viremia can be controlled, a robust anti-p24 Th response can be maintained

Gag( )	p24( )	HIV-1 infection	human( )	[Rosenberg1998]

- Strong Th responses have been found in rare individuals who effectively maintain low viral loads
- If aggressive anti-retroviral therapy is given prior to sero-conversion, strong helper responses can be maintained

Gag( )	p17( )	Vaccine	murine( )	[Birk1998a]

Vaccine: *Vector/type:* recombinant protein *HIV component:* p17

- Different p17 genes derived from the same quasispecies and expressed and purified in *E. coli* primed different Th1 and Th2 subsets in mice, depending on their H-2 type

Gag( )	Gag( )	HIV-1 infection	human( )	[Schiller2000]

- Study of parameters that might influence the performance or reproducibility of clinical Th proliferative assays
- HIV-1 replication *in vitro* is unlikely to influence the assay
- Gag proteins including p17 and possibly p7 as well as p24 perform better than p24 alone
- Frozen samples can be used in T-proliferative assays, but with lower radiolabled thymidine incorporation

Gag( )	Gag( )	HIV-1 infection	human( )	[Pitcher1999a]

- In contrast to earlier studies suggesting that HIV-1 specific Th responses were eliminated in the early stages of infection in most HIV+ individuals, this paper shows using flow cytometric detection of antigen-induced cytokines that Th1 CD4+ memory gag-specific Th cells are detectable in most HIV+ subjects

- Effective anti-viral therapy reduces the frequency of these cells, presumably due to reduced antigenic stimulus

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Gag( ) Gag( ) HIV-1 infection human( ) [Plana1998]

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses

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Gag( ) Gag( ) HIV-1 infection human( ) [Kelleher1998a]

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL-2 therapy – while IL-2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses

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Gag( ) Gag( ) Vaccine Macaca nemestrina( ) [Kent1998a]

Vaccine: *Vector/type:* DNA prime with vaccinia boost *Strain:* LAI *HIV component:* Env, Gag

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env – The Th response happened despite a fall in Ab titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced

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Gag( ) ( ) Vaccine Rhesus macaque( ) [Heeney1999b]

Vaccine: *Vector/type:* DNA, protein, virus-like particle, ISCOM

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge
- Protection correlated with the magnitude of NAb responses, β-chemokines, and a balanced Th response
- DNA, protein+adjuvant, VLP and ISCOM vaccines were tested
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced β-chemokine production

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Gag( ) Gag/Pol( ) Vaccine chimpanzee( ) [Kim1998d]

Vaccine: *Vector/type:* DNA *Strain:* MN *HIV component:* Gag, Pol, Env *Stimulatory Agents:* CD80 and CD86 expression vectors

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses

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Gag( ) Gag/Pol( ) Vaccine human( ) [Salmon-Ceron1999a]

Vaccine: *Vector/type:* canarypox *Strain:* MN, LAI *HIV component:* gp120, gp41, Gag, Protease

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers

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Gag( ) p55( ) HIV-1 infection human( ) [Zhang2001]

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient

- Untreated patients showed a negative correlation between plasma viral load and HIV p24-specific T-cell responses, and the responses could be detected after extended HAART therapy with viremia below the detection limit

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Gag( ) p24( ) HIV-1 infection human( ) [Carcelain2001]

- Repeated structured HAART therapy interruptions (STI) in 3 chronically HIV infected patients induced rapid but transient (< 3 weeks) HIV-1 specific CD4+ Th1 responses concurrently with viral rebound, as measured by proliferation assays and by IFNγ production by CD8-depleted PBMC
- Kinetics suggest that viral replication leads to rapid destruction of the HIV-specific Th1 cell response
- HIV-specific CD8+ T-cell responses were delayed relative to the Th1 responses and were not sustained

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Gag( ) Gag( ) HIV-1 infection human( ) [Blankson2001a]

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy experienced immune reconstitution, and displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T-cells

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Gag( ) p24( ) HIV-1 infection human( ) [Angel2001]

- Prolonged viral suppression resulting from potent anti-retroviral therapy allowed a T-helper response to Gag p24 and PHA to develop in many HIV+ patients
- At baseline, 2/41 (4.9%) subjects had a proliferative response to Gag p24, and 7/41 (17.1%) had a response to PHA, but by week 72 of therapy, 53% had a detectable response to p24 and 94% to PHA

Gag( ) p24( ) HIV-1 infection human( ) [Blazevic2000]

- Prolonged viral suppression resulting from potent anti-retroviral therapy did not allow an HIV T-helper response increase to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients

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Gag( ) Gag( ) HIV-1 infection human( ) [Altfeld2001b]

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T-helper response, and a less diverse viral population than was seen in individuals treated during chronic infection
- The breadth and specificity of the CTL response was determined using Elispot by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef
- Individuals who were given HAART during acute or early in infection had significantly stronger proliferative responses than individuals who were chronically infected

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Gag( ) p24( ) HIV-1 infection human( ) [Oxenius2000b]

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable

- In 3/4 responders tested p24 gave the strongest T-helper response

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Gag( ) p24( ) Vaccine rat( ) [Moss2001]

Vaccine: *Vector/type:* gp120 depleted whole killed virus *Strain:* HZ321 (subtype A env, subtype G gag) *HIV component:* whole virus *Stimulatory Agents:* CpG, Freund's adjuvant

- Lewis rats simultaneously immunized with HIV-1 antigen and with immunostimulatory sequences CpG had increased Th proliferative responses, but when CpG was given as a prime prior to the injection of HIV-1 antigen it was not as effective

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Gag( ) p24( ) Vaccine rat( ) [Moss2000]

Vaccine: *Vector/type:* gp120 depleted whole killed virus *Strain:* HZ321 (subtype A env, subtype G gag) *HIV component:* whole virus *Stimulatory Agents:* CpG, Freund's adjuvant

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFNγ expressing CD4+ and CD8+ T-cells and anti-p24 antibodies relative to antigen in Freund's without CpG

Gag( ) p24( ) *in vitro* stimulation human(A*0201) [Engelmayer2001]

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific IFNγ CD4+ helper T-cell responses to Gag from bulk or purified CD4+ T-cells

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Gag( ) p24( ) Vaccine murine(H-2^d) [Qiu2000a]

Vaccine: *Vector/type:* DNA *HIV component:* Gag

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors
- IFN-γ levels were increased compared to an undetectable IL-4 response
- CTL levels were also increased in secreted Gag expression vaccination studies

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Gag( ) Gag( ) Vaccine murine(H-2^d) [BillautMulot2001]

Vaccine: *Vector/type:* DNA with DNA boost, DNA with recombinant protein boost *Strain:* LAI *HIV component:* Gag, Tat, Nef *Stimulatory Agents:* IL-18

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL-18 showed lymphoproliferative responses 7 weeks post immunization
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFNγ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable
- Co-administration of IL-18 increased T-cell responses but decreased anti-HIV antibody levels

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Gag( )	p24( )		Vaccine	murine(H-2^d)	[Halim2000]

Vaccine: *Vector/type:* coxsackievirus *HIV component:* partial p24, polyepitope

- An avirulent rec coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T-helper responses can be elicited from peptides embedded in a surface loop of the VP1 capsid
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata2001]

Vaccine: *Vector/type: Listeria monocytogenes* *Strain:* HXB2 *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag
- Gag-specific CTL may enhance viral clearance via IFNγ secretion, but are not essential for immunity

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Gag( )	Gag( )	none	Vaccine	murine(H-2^d, H-2^b)	[Mata2000]

Vaccine: *Vector/type: Listeria monocytogenes* *HIV component:* Gag

- BALB/c and C57BL/6 mice were immunized with rec *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways
- This article is a review of *L. monocytogenes* biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response

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